BJS10601

Systematic review of management of chronic pain after surgery

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Appendix S1 Search terms

MEDLINE (Ovid) (1946 to 23 March 2016)

1. randomized controlled trial/ or randomized controlled trial.pt.

2. controlled clinical trial.pt.

3. randomized.ab.

4. placebo.ab.

5. randomly.ab.

6. trial.ab.

7. randomised.tw.

8. 1 or 2 or 3 or 4 or 5 or 6 or 7

9. Pain, Postoperative/

10. ((postoperative adj6 pain*) or (post-operative adj6 pain*) or postoperative- pain*).mp.

11. ((post-operative adj6 analg*) or (postoperative adj6 analg*)).mp.

12. ((post-surgical adj6 pain*) or (post surgical adj6 pain*) or (postsurgery adj6 pain*) or (post adj surg* adj pain*)).mp.

13. ((post* adj pain*) or pain relief after or pain following surg*).mp.

14. ((posttreatment adj6 pain*) or (pain control after adj6 surg*) or ((post-extraction or postextraction or post-surg*) and (pain* or discomfort))).mp.

15. ((analg* adj6 postoperat*) or (analg* adj6 post-operat*) or (pain* adj6 after surg*) or (pain* adj6 after operat*) or (analgesi* adj6 after operat*)).mp.

16. ((pain* or analg*) adj6 ("follow* operat*" or "follow* surg*")).mp.

17. 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16

18. exp Neuralgia/

19. (neuralgia* or neurodynia).tw.

20. ((neuropathic or nerve*) adj3 pain*).tw.

21. Amputation/

22. Phantom Limb/

23. Failed Back Surgery Syndrome/

24. 18 or 19 or 20 or 21 or 22 or 23

25. (chronic* or constant* or continu* or persist* or longterm or long-term or longstanding or long-standing or long lasting or longlasting or phantom).mp.

26. exp Pain, Intractable/ or exp Chronic Pain/

27. exp pain/ and (chronic* adj5 pain*).mp.

28. 25 or 26 or 27

29. 17 or 24

30. 24 or 28

31. 8 and 29 and 30

EMBASE (Ovid) (1980 to 23 March 2016)

1. Randomized controlled trial/ or Randomization/ or Single blind procedure/ or Double blind procedure/ or Crossover procedure/ or Placebo/ or Randomised controlled trial$.tw. or Randomized controlled trial$.tw. or RCT.tw. or Random allocation.tw. or Randomly allocated.tw. or Allocated randomly.tw. or (allocated adj2 random).tw. or Single blind$.tw. or Double blind$.tw. or ((treble or triple) adj blind$).tw. or Placebo$.tw.

2. Pain, Postoperative/

3. ((postoperative adj6 pain*) or (post-operative adj6 pain*) or post-operative-pain*).mp.

4. ((post-operative adj6 analgesi*) or (postoperative adj6 analgesi*)).mp.

5. ((post-surgical adj6 pain*) or (post surgical adj6 pain*) or (post-surgery adj6 pain*) or (post adj surg* adj pain*)).mp.

6. ((post* adj pain*) or pain relief after or pain following surg*).mp.

7. ((posttreatment adj6 pain*) or (pain control after adj6 surg*) or ((post-extraction or postextraction or post-surg*) and (pain* or discomfort))).mp.

8. ((analgesi* adj6 postoperat*) or (analgesi* adj6 post-operat*) or (pain* adj6 after surg*) or (pain* adj6 after operat*) or (analgesi* adj6 after operat*)).mp.

9. ((pain* or analgesi*) adj6 ("follow* operat*" or "follow* surg*")).mp.

10. 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9

11. exp Neuralgia/

12. (neuralgia* or neurodynia).tw.

13. ((neuropathic or nerve*) adj3 pain*).tw.

14. 11 or 12 or 13

15. (chronic* or constant* or continu* or persist* or longterm or long-term or longstanding or long-standing or long lasting or long-lasting or phantom).mp.

16. exp chronic pain/ or exp intractable pain/

17. (chronic* adj5 pain*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]

18. (chronic* adj5 discomfort).mp.

19. (chronic* adj5 ache*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]

20. exp pain/ and (chronic* adj5 pain*).mp.

21. (chronic* adj5 neuralgi*).mp.

22. 15 or 16 or 17 or 18 or 19 or 20 or 21

23. 10 or 14

24. 14 or 22

25. 1 and 23 and 24

26. limit 25 to yr="1902 - 2013"

27. Randomized controlled trial/ or Randomization/ or Single blind procedure/ or Double blind procedure/ or Crossover procedure/ or Placebo/ or Randomised controlled trial$.tw. or Randomized controlled trial$.tw. or RCT.tw. or Random allocation.tw. or Randomly allocated.tw. or Allocated randomly.tw. or (allocated adj2 random).tw. or Single blind$.tw. or Double blind$.tw. or ((treble or triple) adj blind$).tw. or Placebo$.tw.

28. Pain, Postoperative/

29. ((postoperative adj6 pain*) or (post-operative adj6 pain*) or post-operative-pain*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]

30. ((post-operative adj6 analg*) or (postoperative adj6 analg*)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]

31. ((post-surgical adj6 pain*) or (post surgical adj6 pain*) or (post-surgery adj6 pain*) or (post adj surg* adj pain*)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]

32. ((post* adj pain*) or pain relief after or pain following surg*).mp.

33. ((posttreatment adj6 pain*) or (pain control after adj6 surg*) or ((post-extraction or postextraction or post-surg*) and (pain* or discomfort))).mp.

34. ((analg* adj6 postoperat*) or (analg* adj6 post-operat*) or (pain* adj6 after surg*) or (pain* adj6 after operat*) or (analg* adj6 after operat*)).mp.

35. ((pain* or analg*) adj6 ("follow* operat*" or "follow* surg*")).mp.

36. 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35

37. exp Neuralgia/

38. (neuralgia* or neurodynia).tw.

39. ((neuropathic or nerve*) adj3 pain*).tw.

40. failed back surgery syndrome/

41. amputation/

42. phantom limb.mp.

43. 37 or 38 or 39 or 40 or 41 or 42

44. (chronic* or constant* or continu* or persist* or longterm or long-term or longstanding or long-standing or long lasting or long-lasting or phantom).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]

45. exp chronic pain/ or exp intractable pain/

46. exp pain/ and (chronic* adj5 pain*).mp.

47. 44 or 45 or 46

48. 36 or 43

49. 43 or 47

50. 27 and 48 and 49

51. 50 not 26

PsycINFO (inception [1806] to 23 March 2016

1. exp Treatment Effectiveness Evaluation/

2. exp Treatment Outcomes/

3. exp PLACEBO/

4. exp Followup Studies/

5. ((((((((((placebo* or random* or "comparative stud*" or clinical) adj3 trial*) or research) adj3 design) or evaluat*) adj3 stud*) or prospectiv*) adj3 stud*) or (singl* or doubl* or trebl* or tripl*)) adj3 (blind* or mask*)).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]

6. 1 or 2 or 3 or 4 or 5

7. ((postoperative adj6 pain*) or (post-operative adj6 pain*) or post-operative-pain*).mp.

8. ((post-operative adj6 analg*) or (postoperative adj6 analg*)).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]

9. ((post-surgical adj6 pain*) or (post surgical adj6 pain*) or (post-surgery adj6 pain*) or (post adj surg* adj pain*)).mp.

10. ((post* adj pain*) or pain relief after or pain following surg*).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]

11. ((posttreatment adj6 pain*) or (pain control after adj6 surg*) or ((post-extraction or postextraction or post-surg*) and (pain* or discomfort))).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]

12. ((analg* adj6 postoperat*) or (analg* adj6 post-operat*) or (pain* adj6 after surg*) or (pain* adj6 after operat*) or (analg* adj6 after operat*)).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]

13. ((pain* or analg*) adj6 ("follow* operat*" or "follow* surg*")).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]

14. 7 or 8 or 9 or 10 or 11 or 12 or 13

15. exp NEURALGIA/

16. (neuralgia* or neurodynia).tw.

17. ((neuropathic or nerve*) adj3 pain*).tw.

18. failed back surgery.mp.

19. exp AMPUTATION/

20. exp Phantom Limbs/

21. 15 or 16 or 17 or 18 or 19 or 20

22. exp Chronic Pain/

23. (chronic* or constant* or continu* or persist* or longterm or long-term or longstanding or long-standing or long lasting or long-lasting or phantom).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]

24. exp pain/ and (chronic* adj5 pain*).mp.

25. 22 or 23 or 24

26. 14 or 21

27. 21 or 25

28. 6 and 26 and 27

CINAHL (EBSCOHOST) (1982 to 23 March 2016)

Limiters - Exclude MEDLINE records

S35 S8 AND S32 AND S33

S34 S8 AND S32 AND S33

S33 S23 OR S31

S32 S22 OR S23

S31 S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30

S30 (chronic* N5 neuralgi*)

S29 (MH "Pain") and (chronic* N5 pain)

S28 (chronic* N5 ache*)

S27 (chronic* N5 discomfort)

S26 (chronic* N5 pain*)

S25 (MH "Chronic pain")

S24 (chronic* or constant* or continu* or persist* or longterm or long-term or longstanding or long-standing or long lasting or long-lasting or phantom)

S23 S16 OR S17 OR S18 OR S19 OR S20 OR S21

S22 S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15

S21 (MH "Phantom Pain")

S20 (MH "Failed Back Surgery Syndrome")

S19 (MH "Amputation")

S18 ((neuropathic or nerve*) N3 pain*)

S17 (neuralgia* or neurodynia)

S16 (MH "Neuralgia")

S15 ((pain* or analg*) N6 ("follow* operat*" or "follow* surg*"))

S14 ((analg* N6 postoperat*) or (analg* N6 post-operat*) or (pain* N6 after surg*) or (pain* N6 after operat*) or (analg* N6 after operat*))

S13 ((posttreatment N6 pain*) or (pain control after N6 surg*) or ((post-extraction or postextraction or post-surg*) and (pain* or discomfort)))

S12 (post* N2 pain*) or (pain relief after surg*) or (pain following surg*)

S11 ((post-operative N6 analg*) or (postoperative N6 analg*) or (post-surgical N6 pain*) or (post surgical N6 pain*) or (post-surgery N6 pain*) or (post N2 surg* N2 pain*))

S10 ((postoperative N6 pain*) or (post-operative N6 pain*) or post-operative-pain*)

S9 (MH "Postoperative Pain")

S8 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7

S7 AB trial$

S6 AB randomly

S5 AB randomised OR randomized

S4 (MH "clinical trials")

S3 clinical trials

S2 (MH "randomized controlled trials")

S1 randomized controlled trials

Cochrane Library (Wiley) inception to 23 March 2016 in CENTRAL; inception to 29 September 2016 in CDSR

#1 ((postoperative near pain$) or (post-operative near pain$) or post-operative-pain$ or (post$ near pain$) or (postoperative near analg$) or (post-operative near analg$) or ("post-operative analg$"))

#2 ((post-surgical near pain$) or ("post surgical" near pain$) or (post-surgery near pain$))

#3 (("pain-relief after surg$") or ("pain following surg$") or ("pain control after"))

#4 (("post surg$" or post-surg$) and (pain$ or discomfort))

#5 ((pain$ adj4 "after surg$") or (pain$ adj4 "after operat$") or (pain$ adj4 "follow$ operat$") or (pain$ adj4 "follow$ surg$"))

#6 ((analgesi$ adj4 "after surg$") or (analgesi$ adj4 "after operat$") or (analgesi$ adj4 "follow$ operat$") or (analgesi$ adj4 "follow$ surg$"))

#7 failed back surgery

#8 phantom limb

#9 amputation

#10 Chronic$ or constant$ or continu$ or persist$ or longterm or long-term or longstanding or long-standing or long lasting or long-lasting or phantom

#11 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9

#12 #10 and #11

OpenGrey (www.opengrey.eu/)

OpenGrey has limited search options. Two strings were used:

random* AND pain* (no relevant results)

(post-operative OR postoperative) pain (no relevant results)

Table S1 Characteristics of included studies evaluating pharmacological interventions

Study **Country** **Date** **Study design**	**Inclusion criteria** **Patients (number randomized, age, gender)**	**Intervention treatment**	**Control treatment**	**1.) Latest follow-up** **2.) List of outcomes** **3.) Losses to follow-up (intervention/control)** **4.) Results for pain outcome at final follow-up**
Antidepressants				
Kalso et al, 1995 [42] Finland Dates not reported 2 arm cross-over trial	Neuropathic pain after surgical treatment for breast cancer and pain intensity at least moderate N=20 56 years 100% female	Amitriptyline tablets, titrated from 25mg to 100mg/day for 4 weeks	Placebo tablet	1.) 4 weeks 2.) Pain intensity in breast scar region and ipsilateral arm (VRS), pain relief (VRS), disturbance of sleep by pain, McGill Pain Questionnaire, occurrence and severity of adverse effects (VAS), effect of pain on daily life, number of activities disturbed by pain, anxiety (STAI), depression 3.) 5 patients withdrawn (25%) 4.) Lower VRS pain intensity scores in breast scar region ($p<0.05$) and in ipsilateral arm ($p<0.05$) in the intervention group compared to control
Robinson et al, 2004 [39] USA	Pain for ≥3 months after amputation with average pain rating of 2/10 in past month	Amitriptyline tablets, titrated from10mg to 125mg/day for 6 weeks	Active placebo tablet – benztropine mesylate 0.5mg /day	1.) 6 weeks 2.) Pain intensity (NRS), Short-form McGill Pain Questionnaire, occurrence and severity of adverse events, Modified Brief Pain Inventory Pain Interference scale,

Dates not reported 2 arm trial	N=39 (20:19) 44:45 years 15:10% female			depression (CES-D), Functional Independence Measure, Craig Handicap Assessment and Reporting Technique 3.) 2 (2:0) patients withdrawn (5%) 4.) No differences in pain intensity between the groups when controlling for initial pain scores
Tasmuth et al, 2002 [41] Finland Dates not reported 2 arm cross-over trial	Neuropathic pain after treatment for breast cancer and pain intensity at least moderate. N=15 55 years 100% female	Venlafaxine tablets, titrated from 18.75mg to 75mg/day for 4 weeks	Placebo tablet	1.) 4 weeks 2.) Pain intensity (VRS), pain relief (VRS and VAS), occurrence and severity of adverse events (VAS and VRS), anxiety (STAI), depression (BDI) 3.) 2 patients withdrawn (13%) 4.) No difference in the average pain intensities during the last 3 days on the maximum tolerated dose between the intervention and control group
Wilder-Smith et al, 2005 [40]* Mozambique Dates not reported 3 arm trial with open comparator group (amitriptyline)	Phantom limb pain +/- stump pain after amputation with average pain intensity of ≥30/100 in past week N=103 (33:31:30[data provided for 94 patients only]) 41:37:34 years 9:13:10% female	Amitriptyline tablets, titrated from 25mg to 75mg/day for 4 weeks (open comparator arm)	Placebo tablet	1.) 4 weeks (although trial only randomized to day 3) 2.) Phantom and stump pain intensity (VAS), pain duration, general function, global improvement in quality of life and function 3.) 9 patients withdrawn (9%) 4.) No significant differences between treatment groups in changes from baseline in phantom limb and stump pain after one month of treatment in final responders group
Anti-epileptics				

Biyik et al, 2009 [46] Turkey Dates not reported 2 arm trial	Post-sternotomy chest pain or paresthesia lasting ≥3 months and time ≥3 months after sternotomy. N=108 (54:54) 61:59 years 41:59% female	Gabapentin tablets, 800mg/day for 30 days	Diclofenac potassium tablets, 75mg/day	1.) 3 months 2.) Intensity of chest pain and paresthesia (VAS), side effects 3.) 0 patients withdrawn 4.) Pain severity was lower in the intervention group compared to the control group (p<0.001)
Bone et al 2002 [44] UK 1999-2000 2 arm cross-over trial	Phantom limb pain for minimum of 6 months after amputation and pain score of ≥40/100 on VAS N=19 56 years 21% female	Gabapentin tablets, titrated from 300mg to 2400mg/day for 6 weeks	Placebo tablets	1.) 6 weeks 2.) Pain intensity (VAS and categorical), activities of daily living (Barthel index), depression and anxiety (HADS), adverse effects 3.) 5 patients withdrawn (26%) 4.) No differences up to week 5. At week 6 pain lower in intervention group than control (p=0.03)
Hoseinzade et al, 2008 [45]* Iran 2003-2006 2 arm trial	Pain after lumpectomy, mastectomy or modified radical mastectomy for breast cancer N=60 (30:30) Age not reported 100% female	Gabapentin tablets, titrated from 900mg to 1800mg/day for up to 8 weeks	Bupivacaine stellate ganglion block – 8ml of 0.25% bupivacaine injected under guided fluoroscopy. Performed every 5 days for maximum of 5 blocks	1.) 3 months 2.) Pain intensity (NRS), pain location, pain onset, pain quality, satisfaction with life, difficulties with activities of daily living, quality of sleep (all NRS) 3.) Not reported 4.) Pain scores lower in intervention group compared with control group (p<0.001)

Khosravi et al, 2014 [48] Iran Dates not reported 2 arm trial	Chronic leg and back pain after elective lumber discectomy or spinal fusion surgery N=40 (20:20) 47:49 years 55:60% female	Gabapentin tablets, titrated from 300mg to 1800mg/day for 6 months	Naproxen tablets, titrated from 250mg to 1500mg for 6 months.	1.) 32 weeks 2.) Back pain intensity (VAS), leg pain intensity (VAS), amount of rescue medication 3.) 0 patients withdrawn 4.) 27% reduction in VAS back pain in intervention group compared with 22% increase in control group
Silverman et al 2012 [50] USA 2005-2008 2 arm trial followed by open label phase	History of abdominal surgery and adhesions within the previous 5 years. Abdominal pain for > 3 months with a pain intensity of ≥ 40/100 on VAS N=18 (11:7) 44:49 years 100% female	Pregabalin tablets, increased from 150mg/day to 300mg/per day if no pain relief after 3 days. Taken for 7 weeks	Placebo tablets	1.) 7 weeks 2.) Pain intensity (11 point scale), adverse effects 3.) 5 (3:2) patients withdrawn (28%) 4.) Decrease in pain score significantly greater in intervention group compared with control group (p=0.024)
Smith et al, 2005 [43] USA Dates not reported 2 arm cross-over trial	Amputation at least 6 months prior and average pain rating in last month of ≥3/10 on NRS N=24 52 years	Gabapentin tablets, titrated from 300mg to 3600mg/day for 6 weeks	Placebo tablet of lactose	1.) 6 weeks 2.) Phantom limb pain and residual limb pain intensity (NRS), meaningfulness of change in pain, temporal pattern of pain, overall benefit of study medication, modified version of BPI interference scale, Short form McGill Pain Questionnaire, depression (CES-D), Functional Independence Measure, Satisfaction with Life Scale, Craig Handicap Assessment and

	25% female			Reporting Technique (CHART) 3.) Not reported 4.) No difference in phantom limb pain or residual limb pain between intervention and control group
Vilholm et al, 2008 [49] Denmark 2004-2006 2 arm cross-over trial	Post-mastectomy pain syndrome ≥6 months after surgery for breast cancer. Pain duration of ≥ 3 months and pain present at least 4 days a week with a rating of ≥4/10 N=27 60 years 100% female	Levetiracetam tablets, titrated from 500mg to 3000mg/day for 4 weeks	Placebo tablets	1.) 4 weeks 2.) Pain relief (NRS), total pain (NRS), specific pain symptoms (NRS), adverse effects, Quantitative Sensory Testing 3.) 2 patients withdrawn (7%) 4.) No difference in the rating of pain relief between intervention group and control group (p=0.83)
Zencirci et al, 2010 [47] Turkey Dates not reported 2 arm trial	Primarily leg pain after spinal surgery N=42 (21:21) 48:42 years 52:57% female	Gabapentin tablets (1200mg/day) for 1 month, in addition to lumber epidural injection of methylprednisolone acetate followed by an oral treatment containing naproxen sodium, tizanidine and vitamin B and C complex for 1 month	Lumber epidural injection of methylprednisolone acetate followed by an oral treatment containing naproxen sodium, tizanidine and vitamin B and C complex for 1 month	1.) 6 months 2.) Pain on straight leg raise to 45° (VAS), side effects 3.) Not reported 4.) Pain lower in intervention group compared with control group (p<0.001)

Capsaicin				
Bischoff et al 2014 [51] Denmark 2012-2013 2 arm trial	Pain after inguinal herniorrhaphy for >6 months and rated as ≥5/10 on NRS N=46 (24:22) 52:55 years 17:0% female	Capsaicin patch (capsaicin 640μg/cm^2, 8% w/w)	Placebo patch	1.) 3 months 2.) Pain intensity (NRS), neuropathic pain (LANSS), depression and anxiety (HADS), Pain Catastrophizing Scale, Daily Sleep Interference Scale, Quantitative Sensory Testing, skin biopsies, adverse events 3.) 4 (2:2) patients withdrawn (9%) 4.) No difference in summed pain intensity differences between intervention and control group (p=0.29)
Ellison et al 1997 [53] USA 1991-1995 2 arm cross-over trial (only first 8 week period used in this review)	Neuropathic pain after surgery for cancer for >3 months and ≥ moderate intensity N=103 (51:52) 63:64 years 73:72% female	Capsaicin cream (0.075%) 4 times per day for 8 weeks	Placebo cream	1.) 8 weeks 2.) Pain intensity (VAS/Likert), pain relief, pain interference with activities of life, adverse effects 3.) 4 (2:2) patients withdrawn (4%) 4.) Pain relief greater in intervention group compared with control group (p=0.005)
Watson et al 1992 [52] Canada Dates not reported 2 arm trial	Pain after mastectomy for >3 months and ≥ moderate intensity N = 25 (14:11) 56:58 years 100% female	Capsaicin cream (0.075%) 4 times per day for 6 weeks	Placebo cream	1.) 6 weeks 2.) Pain intensity (VAS and verbal intensity scale), pain relief, disability, Quantitative Sensory Testing, adverse events 3.) 7 (3:4) patients withdrawn (28%) 4.) A change from baseline to week 6 was seen in the intervention group (p=0.03) but not the control group. No difference in pain intensity between the treatment and control

				groups (p=0.40)
Epidural steroid injections and associated interventions				
Aldrete, 2003 [63] USA Dates not reported 3 arm trial	Recurrent low back pain (>7/10 on VAS) after one or two lumbar laminectomies, at least 6 months after surgery N=206 (64:60:82) Age and gender not reported	Group 1: Epidural injection of 1 mg of lyophilized, preservative-free indomethacin Na trihydrated powder diluted into 3 mL of 0.5% bupivacaine at baseline and 2 weeks later. Group 2: Epidural injection of 2 mg of lyophilized, preservative-free indomethacin Na trihydrated powder diluted into 3 mL of 0.5% bupivacaine at baseline and 2 weeks later.	Epidural injection of 80 mg of methylprednisolone diluted into 3 mL of 0.5% bupivacaine at baseline and 2 weeks later.	1.) 2 weeks after second injection 2.) Pain intensity (VAS), physical activities, medication needs, emotional status (all assessed with the Pain Progress Score), adverse events 3.) Not reported 4.) Similar changes in pain between groups.
Chun-Jing et al, 2012 [64] China 2006-2009 2 arm trial	Chronic leg pain, with or without back pain after surgery for at least 6 months N=92 (46:46) 59:58 years	Percutaneous lysis involving 50-80ml saline quickly injected into epidural anterior space, followed by 10mg dexamethasone	Puncture to the epidural anterior space for angiography and an injection of 10 mg dexamethasone	1.) 6 months 2.) Low back pain and leg symptoms (VAS), MacNab evaluation, adverse events 3.) 16 (8:8) patients withdrawn (17%) 4.) Pain lower in intervention group compared to control groups (p<0.001)

	45:49% female			
Kim et al, 2012 [61] Korea 2010 3 arm trial	Low back pain or lower extremity radiating pain that recurred after spinal surgery N=65 (23:20:22) 62:64:61 years 48:55:65% female	Interlaminar lumbar epidural injection of a mixture of 1500 IU hyaluronidase, 2 ml triamcinolone 40 mg/ml and 5 ml bupivacaine 0.25%.	Group 1: Interlaminar lumbar epidural injection of 2 ml triamcinolone 40 mg/ml and 5 ml bupivacaine 0.25%. Group 2: Interlaminar lumbar epidural injection of 1500 IU hyaluronidase and 5 ml bupivacaine 0.25%.	1.) 12 weeks 2.) Pain intensity (VAS), Oswestry Disability Index 3.) 5 (0:0:5) patients withdrawn (8%) 4.) Patients in the intervention group reported greater reduction in pain compared to control groups ($p<0.001$)
Manchikanti et al, 2009 [54] USA 2006-2009 2 arm trial	Low back pain with or without lower extremity pain for ≥6 months after lumbar surgery N=120 (60:60) 52:52 years 58:58% female	Percutaneous adhesiolysis with targeted delivery of 5mL lidocaine (2%), 6mL sodium chloride solution (10%), 6mg non-particulate Betamethasone, 1mL sodium chloride solution	Caudal epidural injections with catheterization up to S3 with injection of 5mL lidocaine (2%), 6mL sodium chloride solution (0.9%), 6 mg non-particulate Betamethasone, 1 mL sodium chloride solution	1.) 12 months 2.) Pain intensity (NRS), Oswestry Disability Index, employment status, opioid intake, adverse effects 3.) 35 (2:33) patients withdrawn (58%) 4.) Average pain score lower in intervention group than control group ($p<0.001$)
Manchikanti et al, 2012 [55] USA Started in 2008, ongoing at time of	Cervical post-surgery syndrome involving chronic neck and upper extremity pain for ≥6 months after surgery N=56 (28:28)	Cervical interlaminar epidural injection of 4ml lidocaine (0.5%) and 1ml nonparticulate betamethasone (6mg)	Cervical interlaminar epidural injection of 5ml lidocaine (0.5%)	1.) 12 months 2.) Pain intensity (NRS), Neck Disability Index, work status, opioid treatment, adverse effects 3.) 7 (2:5) patients withdrawn (12.5%) 4.) No difference in pain NRS scores between groups

publication 2 arm trial	49:48 years 32:36% female			(p=0.465)
Manchikanti et al, 2012 [56] USA 2007-2009 2 arm trial	Low back pain with or without extremity pack for ≥6 months after lumbar surgery N=140 (70:70) 48:52 years 49:61% female	Epidural injection of 9ml lidocaine (0.5%) mixed with 1ml of nonparticulate betamethasone (6mg)	Epidural injection of 10ml lidocaine (0.5%)	1.) 24 months 2.) Pain intensity (NRS), Oswestry Disability Index, employment status, opioid intake, adverse effects 3.) 27 (13:14) patients withdrawn (19%) 4.) No difference in pain NRS scores between groups
Meadeb et al, 2001 [57] France Dates not reported 3 arm trial	Sciatica with or without low back pain after discectomy N=58 randomised but data reported for 47 included in analysis (15:16:16) 45:47:43 years 73:50:56% female	Forceful epidural injection of 125mg prednisolone acetate and 20ml saline	Group 1: Forceful epidural injection of 20ml saline Group 2: Epidural injection of 125mg prednisolone acetate	1.) 120 days 2.) Pain intensity (VAS), pain intensity (VAS), Schober's index, finger to floor distance, Dallas questionnaire, adverse effects 3.) 11 patients withdrawn (19%) 4.) No difference in pain VAS scores between groups
Rahimzadeh et al, 2014 [62] Iran Dates not reported	Persistent (>6 months) back pain following laminectomy for spinal canal stenosis and/or discectomy for herniated	Epidural injection of Bupivacaine 5 mg (1 mL), Triamcinolone 40 mg (1mL), Saline solution 10% (2 mL) and	Epidural injection of Bupivacaine 5 mg (1 mL), Triamcinolone 40 mg (1mL), Saline solution 10% (2 mL) and 1 mL	1.) 4 weeks 2.) Pain intensity (VAS), medication use, neurologic examination, straight leg raise, satisfaction with pain control, adverse events

2 arm trial	nucleus pulposus N=25 (12:13) 46:48 years 42:46% female	Hyaluronidase 1,500 IU reconstituted in 1 mL distilled water	distilled water	3.) Not reported 4.) Pain scores were lower in the intervention group compared to the control group (p=0.02)
Revel et al, 1996 [58] France Dates not reported 2 arm trial	Persistent or recurrent lumbosciatic pain after surgery N=60 (29:31) 46:42 years 52:32% female	Forceful epidural injection of prednisolone acetate and saline. Two injections over 48 hours and then 1 per month for 4 months	Simple epidural injection of prednisolone acetate. Two injections over 48 hours and then 1 per month for 4 months	1.) 18 months 2.) Low back and nerve root pain intensity (VAS), function (Waddell's and Main's functional score), Schober's test, finger-to-floor distance, straight-leg raising tests, use of pain medication, satisfaction, adverse events 3.) 19 (14:5) withdrawn (32%) 4.) Greater improvement in lumber pain (p=0.007) but not nerve root pain (p=0.69) in intervention group compared with control group
Rocco et al, 1989 [59]* USA Dates not reported 3 arm trial	Symptomatic after at least one prior laminectomy N=24 (8:8:8) 52:49:50 years 43:50:60% female	Epidural injection with 50mg of lidocaine, 75mg triamcinolone diacetate and 8mg morphine. Three monthly injections.	Group 1: Epidural injection with 50mg of lidocaine, and 8mg morphine Group 2: Epidural injection with 50mg of lidocaine and 75mg triamcinolone diacetate	1.) 6 months for all patients, as long as 2 years for some patients 2.) Pain intensity (VAS), function (results not reported), psychological status (results not reported), adverse effects 3.) 1 patient withdrawn (5%) 4.) No difference in change in pain scores from baseline to 6 months

Yousef et al, 2010 [60] Egypt Dates not reported 2 arm trial	Pain after spinal surgery for ≥ 6 months score ≥6/10 on VAS N=40 (20:20) 49:49 years 33:30% female	Addition of hyaluronidase to fluoroscopically guided caudal epidural steroid and hypertonic saline	Fluoroscopically guided caudal epidural steroid and hypertonic saline without hyaluronidase	1.) 1 year 2.) Pain intensity (VRS), lumbar spine range of motion, opioid intake, adverse events 3.) 2 (2:0) patients withdrawn (5%) 4.) A reduction in pain intensity was observed in the intervention group but not the control group (p<0.05)
Local anaesthetic				
Bischoff et al, 2012 [65] Denmark 2011 2 arm cross-over trial including patients and healthy controls	Pain after inguinal herniorrhaphy for >6 months and pain intensity >6/10 on NRS N=12 48 years 8% female	Lidocaine block - Ultrasound-guided blocks of the ilioinguinal and iliohypogastric nerves with10mls of 1% or 2% lidocaine	Placebo block - Ultrasound-guided blocks of the ilioinguinal and iliohypogastric nerves with 10mls of 0.9% saline	1.) 30 minutes 2.) Pain intensity (NRS), Quantitative Sensory Testing 3.) 0 patients withdrawn 4.) No difference in summed pain intensity differences between groups (p=0.32)
Bischoff et al, 2013 [66] Denmark 2011-2012 2 arm cross-over trial	Pain after inguinal herniorrhaphy for >6 months and pain intensity >6/10 on NRS N=21 57 years 0% female	Lidocaine 5% patches for 14 days	Placebo patch for 14 days	1.) 14 days 2.) Pain intensity (NRS), Daily Sleep Interference Scale, neuropathic pain (LANSS), depression and anxiety (HADS), Pain Catastrophizing Scale, pain relief, sensory mapping, adverse events 3.) 0 patients withdrawn 4.) No difference in summed pain intensity differences between groups (p=0.33)

Casale et al, 2009 [72] Italy Dates not reported 2 arm cross-over trial	Phantom limb pain over the past 6 months N=8 70 years 25% female	Bupivacaine (2.5mg/ml) injected into contralateral muscle areas mirroring the phantom pain	Saline injected into contralateral muscle areas mirroring the phantom pain	1.) 1 hour 2.) Phantom limb pain (VAS), number of painful muscle areas, phantom sensation 3.) 0 patients withdrawn 4.) Pain scores were lower in the intevention group compared to the control group (p=0.003)
Fredman et al, 1999 [68] Israel Dates not reported 2 arm trial	Failed back surgery syndrome after spine surgery N=50 (25:25) 54:54 years 44:52% female	Repeated epidural sympathetic nerve block of 10ml 0.125% bupivacaine twice a day for four days.	Repeated epidural injection of saline twice a day for four days.	1.) 3 months 2.) Pain intensity (VAS), straight leg raise (VAS) 3.) 4 (2:2) patients withdrawn (8%) 4.) No difference in pain intensity scores between groups
Hoseinzade et al, 2008 [45]* Iran 2003-2006 2 arm trial	Pain after lumpectomy, mastectomy or modified radical mastectomy for breast cancer N=60 (30:30) Age not reported 100% female	Bupivacaine stellate ganglion block – 8ml of 0.25% bupivacaine injected under guided fluoroscopy. Performed every 5 days for maximum of 5 blocks	Gabapentin tablets, titrated from 900mg to 1800mg/day for up to 8 weeks	1.) 3 months 2.) Pain intensity (NRS), pain location, pain onset, pain quality, satisfaction with life, difficulties with activities of daily living, quality of sleep (all NRS) 3.) Withdrawals not reported 4.) Pain score lower in gabapentin group compared with bupivacaine group (p<0.001)
Ilfeld et al, 2013 [73] USA Dates not reported	Phantom limb pan and/or residual limb pain with intensity of ≥2/10 in the past week and occurring on a weekly basis over at	Ropivacaine (0.4%) perineural infusion over 6 days. Total of 1,100mL of study fluid.	Normal saline perineural infusion over 6 days. Total of 1,100mL of study fluid.	1.) 12 weeks 2.) Pain intensity (Brief Pain Inventory), pain interference (Brief Pain Inventory), number of times phantom limb pain experienced, worst and average phantom limb pain (NRS),

Pilot 2 arm cross-over trial	least the previous month. N=3 33 years 0% female			Patient Global Impression of Change scale, adverse events 3.) 1 patient withdrawn (33%) 4.) No statistical analysis performed
Kvarnstrom et al, 2003 [69]* Sweden Dates not reported 3 arm cross-over trial	Peripheral nerve or root lesions of traumatic origin, e.g. trauma, surgery or compression N=12 47 years 75% female	Intravenous lidocaine hydrochloride with 1.0mg/kg during 10 mins and then 1.5mg/kg during 30 mins. Diluted in saline and given by infusion using an infusion pump	Intravenous saline solution (Saline (NaCl 9mg/ml)	1.) 150 minutes 2.) Pain (VAS), Quantitative Sensory Testing, adverse events 3.) 0 patients withdrawn 4.) No difference in pain reduction between intervention and control groups (p=0.299)
Liu et al, 2013 [74] China 2011-2012 2 arm trial	Post-operative neuropathic pain after modified radical mastectomy N=48 (24:24) 51:50 years 100% female	Lidocaine stellate ganglion block – 2% lidocaine (0.10g/5ml) with ultrasound guidance	Lidocaine stellate ganglion block – 2% lidocaine (0.10g/5ml) with without ultrasound guidance	1.) 8 weeks 2.) Pain intensity (VAS), adverse effects 3.) 0 patients withdrawn 4.) Pain scores were lower in intervention group compared with control group (p=0.029)
Park et al, 2012 [67] Korea Dates not reported 3 arm cross-over trial	Previous lumbar surgery and neuropathic pain for >2 years N=18	Lidocaine intravenous infusion - 1mg/kg lidocaine in 500ml saline infused over 1 hour	Placebo infusion of 0.9% saline	1.) 24 hours 2.) Pain intensity (VAS), neuropathic pain scales 3.) 0 patients withdrawn 4.) No difference in amount of change in pain between

	43 years 72% female	Lidocaine intravenous injection - 5mg/kg lidocaine in 500ml saline infused over 1 hour		intervention and control group
Wu et al, 2002 [70]* USA 1997-2001 3 arm cross-over trial	Persistent postamputation pain for 6 months after amputation N=32 54 years 39% female	Lidocaine intravenous infusion - 1 mg/kg lidocaine as bolus over 2 minutes, followed by infusion of 4mg/kg lidocaine over 40 minutes. Maximum infusion dose was 400mg lidocaine.	10 mg of diphenhydramine as an intravenous bolus over 2 minutes, followed by an infusion of 40 mg of diphenhydramine over 40 minutes.	1.) 30 minutes 2.) Phantom and stump pain intensity (VAS), sedation scores (VAS), pain relief 3.) 1 patient withdrawn (3%) 4.) Intervention deceased stump pain ($p<0.01$) but not phantom pain ($p>0.05$) compared with control
Wu et al. 2008 [71]* USA 1999-2003 3 arm cross-over trial	Persistent post-amputation pain for ≥6 months rated as > 3/10 on NRS N=60 63 years 22% female	Mexiletine, titrated from 75mg to 1200mg/day over 8 weeks	Placebo tablet	1.) 6 weeks 2.) Pain intensity (NRS), pain relief, interference and general activity scales of the Multidimensional Pain Inventory, adverse effects 3.) 25 patients (42%) did not complete all 3 treatments (10 morphine, 6 mexiletine, 5 placebo; 4 patient withdrawn before treatment) 4.) Average change in pain intensity from baseline was similar in intervention and control group
Neurotoxins				
Singh et al, 2010 [75] USA	Pain after total knee replacement for >3 months and pain intensity	Intra-articular injection of 100 units botulinum toxin A diluted in 5 ml	Intra-articular injection of 5 ml sterile normal	1.) 6 months (2 months was the primary endpoint) 2.) Pain intensity (VAS), adverse events, WOMAC, functional

2006-2009 2 arm trial	≥ 6/10 on NRS N=54 (60 knees) (30:30) 67: 67 years 22:12% female	sterile normal saline	saline	tests, SF-36, Short form McGill Pain Questionnaire, physicians' global assessment of change, timed stands test, timed up and go test, active knee flexion and extension, analgesics 3.) 7 (3:4) patients withdrawn (14%) 4.) 71% of patients in intervention group were responders at 2 months compared to 35% in control group (p=0.025)
Wittekindt et al, 2006 [76] Germany Dates not reported Dose finding 2 arm trial	Chronic neuropathic pain for >12 months after neck dissection N=23 (10:13) 60 years 9% female	Injection of botulinum toxin A reconstituted in saline to a concentration of 20 mouse units/0.1 ml saline.	Injection of botulinum toxin A reconstituted in saline to a concentration of 10 mouse units/0.1 ml saline.	1.) 28 days 2.) Pain intensity (VAS), side effects, global quality-of-life scale (EORTC-QLQ-C-30), symptoms scale "pain" (EORTC-QLQ-H&N35) 3.) 0 patients withdrawn 4.) Patients in the low-dose group improved in self-assessment of pain VAS from day 0 to 28 (p<0.05). No improvement was observed with the high-dose group (p=0.15)
Wu et al, 2012 [77] USA 2005-2007 2 arm pilot trial	Daily residual limb pain and/or phantom limb pain > 5/10 on VAS N=14 (7:7) 47:50 years 43:14% female	Injection of botulinum toxin A reconstituted with 0.9% saline to a concentration of 50 units/mL. Maximum of 6 painful sites injected.	Injection of 1mL mixture of 0.75mL of 1% lidocaine and 0.25mL of Depomedrol 40 mg/mL (10 mg).	1.) 6 months 2.) Phantom limb pain intensity (VAS), residual limb pain (VAS), pressure pain tolerance 3.) 4 (3:1) patients withdrawn (29%) 4.) No difference in phantom limb pain or residual limb pain between groups
NMDA receptor antagonists				

Eichenberger et al, 2008 [78]* Switzerland Dates not reported 3 arm cross-over trial (4th arm added during trial)	Phantom limb pain for at least 6 months with a mean pain intensity of ≥3/10 on VAS N=20 57 years 25% female	Ketamine (0.4mg/kg) and calcitonin (200 IE), each diluted with 0.9% saline to a total volume of 20mL and infused over 1 hour	Two 20mL infusions of 0.9% saline.	1.) 48 hours 2.) Phantom limb pain intensity (VAS), number and intensity of pain attacks, adverse effects 3.) 0 patients withdrawn 4.) Mean pain scores ($p<0.001$) and maximum pain scores ($p=0.001$) lower in intervention group compared with control group
Kvarnstrom et al, 2003 [69]* Sweden Dates not reported 3 arm cross-over trial	Peripheral nerve or root lesions of traumatic origin, e.g. trauma, surgery or compression N=12 47 years 75% female	Intravenous ketamine hydrochloride (0.4mg/kg) infused at a constant rate of 40 minutes. Diluted in saline and given by infusion using an infusion pump	Intravenous saline solution (Saline (NaCl 9mg/ml)	1.) 150 minutes 2.) Pain (VAS), Quantitative Sensory Testing, adverse events 3.) 0 patients withdrawn 4.) Reduction in pain was greater in the intervention group compared with the placebo group ($p=0.009$)
Maier et al, 2003 [79] Germany Dates not reported 2 arm trial	Phantom limb pain for ≥12 months after amputation and pain intensity of ≥4/10 on NRS N=36 (18:18) 62:61 years 78:83% female	Memantine tablets, titrated from 5mg to 30mg/day for 4 weeks	Placebo tablets	1.) 4 weeks 2.) Pain intensity (NRS), severity of adverse events, Pain Disability Index, validated German depression scale, (ADS) 3.) 5 (2:3) patients withdrawn (14%) 4.) Phantom limb pain intensity was similar between the intervention and control group

Nikolajsen et al, 1996 [83] Denmark Dates not reported 2 arm cross-over trial	Postamputation stump and phantom limb pain N=11 47 years 73% female	Ketamine (0.5 mg/kg) diluted in 100ml isotonic NaCl and infused intravenously by an infusion pump.	Saline (0.01 ml/kg, 9 mg/ml NaCl) diluted in 100ml isotonic NaCl and infused intravenously by an infusion pump.	1.) 80 minutes 2.) Phantom limb and stump pain intensity (VAS), McGill Pain Questionnaire, Quantitative Sensory Testing, adverse effects 3.) 0 patients withdrawn 4.) The intervention, but not the control, produced relief of stump pain and phantom pain ($p<0.05$)
Nikolajsen et al, 2000 [82] Denmark 1997-1999 2 arm cross-over trial	Neuropathic pain after amputation or surgery and continuous pain intensity ≥3/10 on NRS N=19 51 years 42% female	Memantine tablets, titrated from 5mg to 20mg for 5 weeks	Placebo tablets	1.) 5 weeks 2.) Stump and phantom pain intensity (NRS), adverse effects, McGill Pain Questionnaire, Quantitative Sensory Testing, compliance 3.) 4 (1:3) patients withdrawn (21%) 4.) No differences in pain intensity between the intervention and control group
Schwenkreis et al, 2003 [81] Germany Dates not reported 2 arm trial	Phantom limb pain for ≥12 months N=16(8:8) 62 years (breakdown by group not provided) 13% female	Memantine tablets, titrated from 5mg to 30mg/day for 3 weeks	Placebo tablets	1.) 3 weeks 2.) Phantom limb pain (NRS), transcranial magnetic stimulation, serum samples 3.) 1 (1:0) patients withdrawn (6%) 4.) No difference in pain reduction between groups
Wiech et al, 2004 [80] Germany Not stated 2 arm cross-over trial	Chronic phantom limb pain after upper limb amputation N=8 45 years	Memantine tablets titrated from 10mg to 30mg/day for 4 weeks.	Placebo tablets	1.) 4 weeks 2.) Phantom limb pain and residual limb pain intensity (VAS), adverse effects 3.) 0 patients withdrawn 4.) No difference between groups in phantom limb pain

	13% female			(p=0.16) or pain in the residual limb (p=0.15)
Opioids				
Huse et al, 2001 [84] Germany Dates not reported 2 arm cross-over trial	Phantom limb pain after amputation with an intensity ≥3/10 on VAS N=12 51 years 17% female	Morphine sulphate infusion titrated to at least 70mg/day and highest of 300mg/day over 4 weeks.	Glucose solution placebo	1.) 4 weeks 2.) Phantom limb and stump pain intensity (VAS), adverse events, Patient Experience Scale, Quantitative Sensory Testing, Self-Rating Depression Scale, Pain-Related Self-Statement Scale, West Haven-Yale Multidimensional Pain Inventory, Brief Stress Scale 3.) 0 patients withdrawn 4.) Pain lower in intervention group compared to control group (p=0.036)
Patarica-Huber et al, 2011[85] Serbia Dates not reported 3 arm trial	Pain after treatment for breast cancer for ≥3 months and rated as ≥5/10 on VAS N=75 (25:25:25) 44 years 100% female	Combination of three drugs: 60mg sustained-release morphine, 900 mg gabapentin, 100mg diclofen per day for 6 weeks	Group 1- gabapentin, maximum dose of 3600 mg/day for 6 weeks Group 2- 1200mg gabapentin and 100mg diclofen per day for 6 weeks	1.) 6 weeks 2.) Pain intensity (VAS and/or Likert Scale), pain relief, influence of pain on daily activities, adverse effects 3.) Withdrawals not reported 4.) Pain intensity not different between intervention and control group (p>0.05)
Rocco et al, 1989 [59]* USA Dates not reported	Symptomatic after at least one prior laminectomy N=22 (7:8:7)	Epidural injection with 50mg of lidocaine, 75mg triamcinolone diacetate and 8mg morphine. Three monthly injections.	Group 1 - Epidural injection with 50mg of lidocaine and 75mg triamcinolone diacetate	1.) 6 months for all patients, as long as 2 years for some patients (although trial was stopped early due to a serious adverse event) 2.) Pain intensity (VAS), function (results not reported), psychological status (results not reported), adverse effects

3 arm trial	52:49:50 years 43:50:60% female		Group 2 - Epidural injection with 50mg of lidocaine, and 8mg morphine	3.) 1 patient withdrawn (4.5%) 4.) No difference in change in pain scores from baseline to 6 months
Wilder-Smith et al, 2005 [40]* 3 arm trial with open comparator group (amitriptyline)	Phantom limb pain +/- stump pain after amputation with average pain intensity of ≥30/100 in past week N=94 (33:31:30) 41:37:34 years 9:13:10% female	100mg slow release tramadol tablets taken twice daily for 4 weeks.	Placebo tablet	1.) 4 weeks 2.) Phantom and stump pain intensity (VAS), pain duration, general function, global improvement in quality of life and function, Quantitative Sensory Testing 3.) 9 patients withdrawn (9%) 4.) No differences between treatment groups in changes from baseline in phantom limb and stump pain after one month of treatment in final responders group
Wu et al, 2002 [70]* USA 1997-2001 3 arm cross-over trial	Persistent postamputation pain for 6 months after amputation N=32 54 years 39% female	0.05 mg/kg of morphine as an intravenous bolus over 2 minutes, followed by an infusion of 0.2 mg/kg of morphine over 40 minutes. Maximum infusion dose of 25 mg of morphine	10 mg of diphenhydramine as an intravenous bolus over 2 mins, followed by an infusion of 40 mg of diphenhydramine over 40 minutes.	1.) 30 minutes 2.) Phantom and stump pain intensity (VAS), sedation scores (VAS), pain relief 3.) 1 patient withdrawn (3%) 4.) Compared to placebo, the intervention reduced stump pain ($p<0.01$) and phantom limb pain intensity ($p<0.001$)
Wu et al. 2008 [71]* USA 1999-2003 3 arm cross-over trial	Persistent post-amputation pain for ≥6 months rated as > 3/10 on NRS N=60	Sustained-release morphine, titrated from 15mg to 180mg/day over 8 weeks	Placebo tablet	1.) 6 weeks 2.) Pain intensity (NRS), pain relief, interference and general activity scales of the Multidimensional Pain Inventory, adverse effects 3.) 25 patients (42%) did not complete all 3 treatments (10

	63 years 22% female			morphine, 6 mexiletine, 5 placebo; 4 patient withdrawn before treatment) 4.) The intervention provided better pain relief when compared with the placebo (p=0.003)
Other pharmacological interventions				
Eichenberger et al, 2008 [78]* Switzerland Dates not reported 3 arm cross-over trial (4th arm added during trial)	Phantom limb pain for at least 6 months with a mean pain intensity of ≥3/10 on VAS N=20 57 years 25% female	Calcitonin (200 IE) diluted with 0.9% saline to a total volume of 20mL and infused over 1 hour	20mL infusions of 0.9% saline.	1.) 48 hours 2.) Phantom limb pain intensity (VAS), number and intensity of pain attacks, adverse effects 3.) 0 patients withdrawn 4.) The intervention did not reduce pain intensity compared with the placebo
Block et al, 2015 [86] Sweden Dates not reported 3 arm trial	Severe long-term pain after surgery treated with morphine infusion N=12 55 years 67% female	Group 1: Addition of naloxone (dose of NAL40) to IT morphine pump for 3 weeks Group 2: Group 1: Addition of naloxone (dose of NAL400) to IT morphine pump for 3 weeks	Sham treatment procedure additional to IT morphine pump for 3 weeks	1.) 3 weeks 2.) Pain intensity (NRS), sleep quality, activity, SF-36, treatment-emergent adverse effects, serious adverse events 3.) 1 patient (8%) withdrawn 4.) None of the interventions were associated with changes in pain

NRS =numerical rating scale; VAS = visual analogue scale; VRS = verbal rating scale

*Included in table twice as evaluating two interventions which fall into different categories

Table S2 Characteristics of included studies evaluating physical, surgical, psychological and other interventions

Study **Country** **Date** **Study design**	**Inclusion criteria** **Patients (number randomized, age, gender)**	**Intervention treatment**	**Control treatment**	**1.) Latest follow-up** **2.) Outcomes** **3.) Losses to follow-up (intervention/control)** **4.) Results for pain data at final follow-up**
Acupuncture / dry needling				
Arias-Buria et al, 2015 [87] Spain 2012-2013 2-arm trial	Pain after shoulder surgery N=20 (10:10) 58:57 years 70:80% female	One session of trigger point dry needling and 5 sessions of physical rehabilitation	5 sessions of physical rehabilitation	1.) 1 week 2.) Constant-Murley total score and subscale scores (pain, activities of daily living, range of motion, strength), adverse events 3.) 0 patients withdrawn 4.) No differences in pain intensity between groups (p=0.124)
Pfister et al, 2010 [88]	Moderate or severe pain at ≥ 3 months after neck	Acupuncture once a week for 4 weeks. Needles	Usual care - entailed no specific treatment,	1.) 42 days 2.) Pain intensity on activity (NRS), Constant-Murley score,

USA 2004-2007 2 arm trial	dissection for cancer N=70 (34:36) 61: 57 years 46:23% female	were inserted in customized and anatomic points using the traditional Chinese medicine acupuncture technique at a depth of 0.25 to 0.5 inches and retained for 30 minutes.	physical therapy, analgesia, and/or anti-inflammatory drugs, per patient preference or physician recommendation	dry mouth (Xerostomia Inventory), adverse events 3.) 12 (6:6) patients withdrawn (17%) 4.) Pain relief greater in intervention group compared with control group (p<0.001)
Exercise				
Brox et al, 2006 [90]* Norway Dates not reported 2 arm trial	Low back pain for ≥ 1 year after surgery for disc herniation and a score ≥ 30/100 on the Oswestry Disability Index N=60 (31:29) 43:42 years 35:62% female	Cognitive intervention and exercises lasting for 25 hours per week for 3 weeks.	Posterolateral fusion with pedicle fixation	1.) 1 year 2.) Back and leg pain intensity (VAS), Oswestry Disability Index, pain medication, General Function Score, emotional distress (Hopkins Symptom Check List-25), Waddell's Fear-Avoidance Belief Questionnaire, Global Back Disability Question, fingertip-floor distance, work status, radiographic fusion, adverse events 3.) 3 (2:1) patients withdrawn 4.) No difference between groups from baseline to 1 year follow-up in back pain (p=0.42) or lower limb pain (p=0.68)
Brunelli et al, 2015 [91] Italy 2011-2013 2 arm trial	Phantom limb pain and/or sensation N=51 (27:24) 59:65 years 30:35% female	Progressive muscle relaxation, mental imagery and phantom exercise training twice a week for 4 weeks	General exercise program in addition to the standard physical therapy, twice a week for 4 weeks	1.) 1 month 2.) Phantom limb pain (Prosthesis Evaluation Questionnaire), Brief Pain Inventory, phantom limb sensation 3.) 11 (7:4) patients withdrawn (22%) 4.) Intensity of phantom limb pain lower in intervention group

				compared to control group (p=0.047)
Manniche et al, 1993 [89] Denmark Dates not reported 2 arm trial	Back pain after lumbar surgery for intervertebral disc protrusion N=62 (31:31) 51:49 years 42:39% female	Intensive exercise programme involving 24 sessions over a 3 month period. Exercises involve trunk lifting, leg lifting, abdominal exercises, pull to the neck. Hyperextension allowed	Same as intervention but hyperextension not allowed	1.) 1 year 2.) Back pain intensity (Low Back Pain Rating Scale), leg pain intensity (Standardised Nordic Questionnaire), disability, physical impairment (back endurance, Schober's modified test patient's mobility), use of analgesics 3.) 15 (5:10) patients withdrawn (24%) 4.) No difference in pain intensity between the intervention and control group (p=0.08)
Timm et al, 1994 [92]* USA 1984-1990 5-arm trial	Chronic low back pain for at least 6 months following single-level lumbar laminectomy of the L5 segment N=150 (50 per arm; 2 exercise arms and control arm) 44:43:45 years 26:30:28% female	Group 1:'Low tech' exercises: 24 sessions over 8 weeks of Mc- Kenzie-type and spinal stabilization training exercises. Group 2. 'High tech' exercises: 24 sessions over 8 weeks of cardiovascular, isotonic, and isokinetic exercise.	No treatment	1.) 8 weeks 2.) Back pain-related disability (Oswestry Disability Index), modified-modified Schober method (lumber range of motion), Cybex Liftask isokinetic lifting dynamometer (functional spinal muscle strength) 3.) 0 patients withdrawn 4.) Improvements in back pain-related disability greater for both interventions groups compared to control group.
Limb covering				

Hsiao et al, 2012 [93] USA 2009-2010 2-arm trial	Phantom limb pain, 3 or more episodes over previous 6 weeks N=57 (30:27) 62:66 years 3:0% female	Farabloc non-invasive limb cover worn continuously for 12 weeks	Sham limb cover worn continuously for 12 weeks	1.) 12 weeks 2.) Phantom limb pain intensity (NRS), overall bodily pain (NRS), phantom limb pain frequency per week and per month, Veterans RAND 12-item Health Survey 3.) 10 (7:3) patients withdrawn (18%) 4.) Mean change in phantom limb pain from baseline to 12 weeks was similar between groups (p=0.38)
Kern et al, 2006 [94] Germany 2005 2 arm cross-over trial	Phantom limb pain rated as ≥3/10 for ≥10 days per month N=30 Age not provided 27% female	Textile, electromagnetically-acting silicon stump liner worn for 2 weeks	Placebo liner worn for 2 weeks	1.) 2 weeks 2.) Phantom limb pain (NRS), wellbeing, sleep quality 3.) 8 patients withdrawn (27%) 4.) Reduction of phantom limb pain was greater in the intervention group compared with the control group (p<0001)
Spinal cord stimulation				
Kumar et al, 2007 [97] Europe, Canada, Australia, Israel 2003-2005 2 arm trial	Neuropathic pain of radicular origin for ≥6 months after surgery for herniated disc and a score of ≥50/100 on VAS N=100 (52:48) 52:49 years 56:42% female	Spinal cord stimulation with implantable neurostimulation system	Conventional medical management (actively managed and at discretion of study investigator)	1.) 6 months 2.) Leg and pain back intensity (VAS), health-related quality of life (SF-36), Oswestry Disability Index, use of pain therapies, patient satisfaction with treatment, adverse events 3.) 6 (2:4) patients withdrawn (6%) 4.) Compared with the control group, patients in the intervention group experienced lower levels of back pain (p = 0.008) and leg pain (p < 0.0001)

North et al, 2005 [95]* USA Dates not reported 2 arm trial with cross-over allowed at 6 months	Persistent or recurrent radicular pain, with or without low back pain after lumbosacral spine surgery N=60(30:30) 50 years 50% female	Spinal cord stimulation with permanent implant	Laminectomy and/or foraminotomy and/or discectomy	1.) 6 months and then minimum of 2 years 2.) Pain intensity (VAS), pain relief, functional capacity, ability to perform activities of daily living, psychological assessment, frequency of cross-over, medication intake, satisfaction with treatment 3.) 1 (1:0) patient withdrawn (2%) 4.) 47% in the spinal cord stimulation group achieved at least 50% pain relief , which was higher than the 12% in the surgery group ($p<0.01$)
Schu et al, 2014 [98] Germany 2013 3 arm cross-over trial	Failed back surgery syndrome N=20 57 years 65% female	Spinal cord stimulation with burst stimulation of 500Hz, delivered 40 times per second for 1 week	Group 1: Tonic stimulation at a frequency of 500Hz for 1 week Group 2: Placebo stimulation (device switched off) for 1 week	1.) 1 week 2.) Pain intensity (NRS), Short-form McGill Pain Questionnaire, treatment preference, Oswestry Disability Index, serious adverse events 3.) 0 patients withdrawn 4.) Pain scores were decreased in the intervention group compared with the two control groups ($p<0.0001$)
Van Gorp et al, 2016 [96] Netherlands 2012-2014 2 arm trial	Neuropathic leg pain combined with chronic lower back pain for >6 months after lumbar spine surgery N=65 (33:32) 47:54 years 32:46% female	Subcutaneous stimulation as add on therapy to spinal cord stimulation for a period of 3 months	Subcutaneous leads switched off	1.) 3 months 2.) Back pain intensity (VAS), leg pain intensity (VAS), adverse events, McGill Pain Questionnaire, SF-36, EQ-5D, Hospital Anxiety and Depression Scale, Oswestry Disability Index, Patient Global Impression of Change, Medication Quantification Scale Version III 3.) 13 (5:8) patients withdrawn (20%) 4.) A greater percentage of patients achieved 50% or more pain

				relief on the back VAS in the treatment group compared with the control group (43% vs 4%; p=0.001). No difference observed for leg pain (21% vs 21%; p=1.000)
Van Havenbergh et al, 2015 [99] Belgium Not reported 2 arm cross-over trial	Failed back surgery syndrome N=15 52 years 47% female	Spinal cord stimulation with 1000-Hz burst mode for 2 weeks	Spinal cord stimulation with 500-Hz burst mode for 2 weeks	1.) 2 weeks 2.) Back pain (VAS), limb pain (VAS), general pain (VAS), paresthesia, Pain Catastrophizing Scale, Pain Vigilance and Awareness Questionnaire, SF-36 3.) 0 patients withdrawn 4.) No difference in back pain (p=0.90) or limb pain (p=0.76) between the groups
Surgery				
Brox et al, 2006 [90]* Norway Dates not reported 2 arm trial	Low back pain for ≥ 1 year after surgery for disc herniation and a score ≥ 30/100 on the Oswestry Disability Index N=60 (29:31) 42:43 years 62:35% female	Posterolateral fusion with pedicle fixation	Cognitive intervention and exercises lasting for 25 hours per week for 3 weeks.	1.) 1 year 2.) Back and leg pain intensity (VAS), Oswestry Disability Index, pain medication, General Function Score, emotional distress (Hopkins Symptom Check List-25), Waddell's Fear-Avoidance Belief Questionnaire, Global Back Disability Question, fingertip-floor distance, work status, radiographic fusion, adverse events 3.) 3 (1:2) patients withdrawn 4.) No difference between groups from baseline to 1 year follow-up in back pain (p=0.42) or lower limb pain (p=0.68)
North et al, 2005 [95]* USA Dates not reported	Persistent or recurrent radicular pain, with or without low back pain after lumbosacral spine	Laminectomy and/or foraminotomy and/or discectomy	Spinal cord stimulation with permanent implant	1.) 6 months and then minimum of 2 years 2.) Pain intensity (VAS), pain relief, functional capacity, ability to perform activities of daily living, psychological assessment, frequency of cross-over, medication intake, satisfaction with

2 arm trial with cross-over allowed at 6 months	surgery N=60(30:30) 50 years 50% female			treatment 3.) 1 (1:0) patient withdrawn (2%) 4.) A lower percentage of patients achieved at least 50% pain relief in the surgery group compared with the spinal cord stimulation group (12% vs 47%; p<0.01)
Other interventions				
Chan et al, 2007 [104] USA Dates not reported 3 arm trial	Phantom limb pain after leg or foot amputation N=22 (breakdown not provided) Age and gender not provided	Mirror therapy for 15 minutes daily for 4 weeks. Involved viewing a reflected image of their intact foot in a mirror and performing movements with the amputated limb.	Group 1: Mirror theory with covered mirror Group 2: Mental visualization - imagined performing movements with eyes closed.	1.) 4 weeks 2.) Phantom limb pain intensity (VAS), number and duration of pain episodes 3.) 4 patients withdrawn (18%) 4.) Patients in the intervention group reported a greater improvement in pain than patients in control group 1(p=0.04) or group 2 (p=0.002)
Ebid et al, 2015 [101] Egypt Dates not reported 2-arm trial	Post mastectomy pain syndrome with unilateral mild-to-moderate lymphedema N=61 (30:31) 53:54 years 100:100% female	Pulsed Nd:YAG laser treatment 3 times a week for four weeks	Placebo laser treatment	1.) 12 weeks 2.) Pain intensity (VAS), shoulder range of motion, quality of life (EORTC QLQ-C30) 3.) 0 patients withdrawn 4.) Pain scores lower in intervention group compared with control group (p=0.0021)

Esmer et al, 2011 [103] USA Dates not reported 2 arm trial	Persistent leg or back pain after lumbosacral spinal surgery N=40 (19:21) 55:55 years 53:30% female	Mindfulness-based stress reduction training for 8 weeks	Waiting list control	1.) 3 months and then (for intervention only) 9 months 2.) Pain intensity (VAS), function (Roland-Morris Disability Questionnaire), pain acceptance and quality of life (Chronic Pain Acceptance Questionnaire), sleep quality (Abridged Pittsburgh Sleep Quality Index), medication intake 3.) 9 (4:5) patients withdrawn (23%) 4.) Patient in the intervention group reported a greater improvement in VAS pain scores compared with the control group (p=0.021)
Flor et al, 2001 [102] Germany Dates not reported 2 arm trial	Phantom limb pain after arm amputation N= 10 (5:5) 54:57 years 20:20% female	Sensory discrimination training, 10 x 90 minute sessions over 2 weeks	Comprehensive psychophysiological assessment, 3 x 4 hours of clinician contact over 2 weeks	1.) 3 months 2.) Phantom limb pain (Yale Multidimensional Pain Inventory), cortical reorganization, ability to discriminate location and frequency of the stimulation 3.) 0 patients withdrawn 4.) Phantom limb pain decreased from pre-training to post-training in the intervention group (p=0.008) whereas there was no change in the control group
Timm et al, 1994 [92]* USA 1984-1990 5-arm trial	Chronic low back pain for at least 6 months following single-level lumbar laminectomy of the L5 segment N=100 (50:50) 42:45 28:28% female	24 sessions over 8 weeks of joint manipulation involving large-amplitude, low-velocity manual therapy procedures to the TI 2-L1 through L5-S1 intervertebral levels .	No treatment	1.) 8 weeks 2.) Back pain-related disability (Oswestry Disability Index), modified-modified Schober method (lumber range of motion), Cybex Liftask isokinetic lifting dynamometer (functional spinal muscle strength) 3.) 0 patients withdrawn 4.) No difference in back pain-related disability between the intervention and control group

Timm et al, 1994 [92]* USA 1984-1990 5-arm trial	Chronic low back pain for at least 6 months following single-level lumbar laminectomy of the L5 segment N=100 (50:50) 42:45 24:28% female	24 sessions over 8 weeks of 'physical agents' including hot packs, ultrasound and TENS	No treatment	1.) 8 weeks 2.) Back pain-related disability (Oswestry Disability Index), modified-modified Schober method (lumber range of motion), Cybex Liftask isokinetic lifting dynamometer (functional spinal muscle strength) 3.) 0 patients withdrawn 4.) No difference in back pain-related disability between the intervention and control group
Weintraub et al, 2005 [100] USA Dates not reported 2 arm trial	Constant back pain after failed surgery N=17 (8:8) 1 patient dropped out but group not reported 54 years 35% female	Active magnetic back corset (350 gauss) and a similar permanent magnetic foot insole (450 gauss) worn for 24 hours.	Similar back and foot sham worn for 24 hours.	1.) 2 months 2.) Pain intensity (VAS), sleep distribution (VAS) 3.) 1 patient withdrawn (6%) 4.) No difference in reduction in VAS pain scores between intervention and control group from baseline to 2 months (p=0.81)

NRS =numerical rating scale; VAS = visual analogue scale; VRS = verbal rating scale

*Included in table twice or more as evaluating interventions which fall into different categories

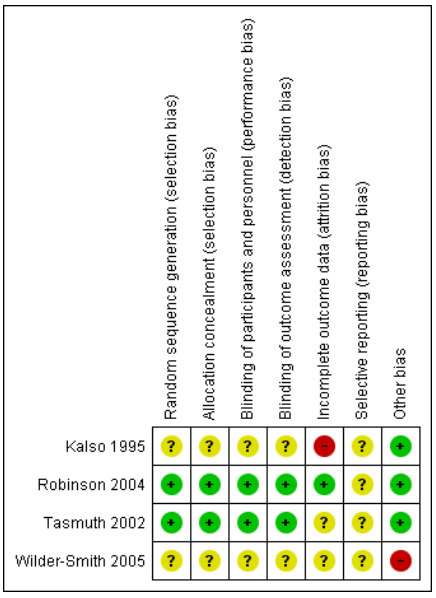
Appendix S2 Risk of bias by intervention type

Risk of bias tables

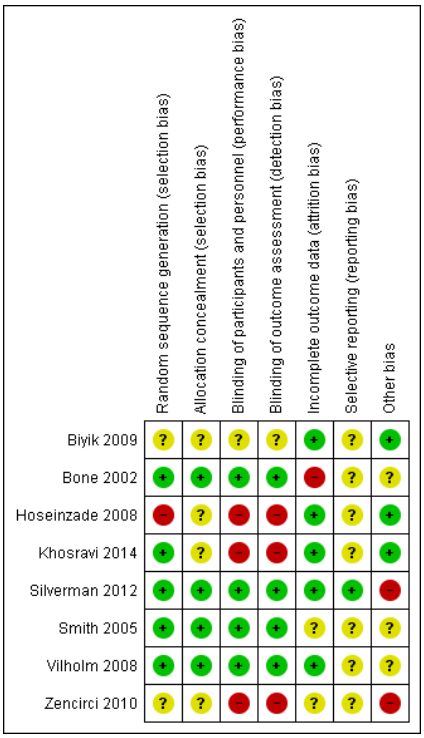
Risk of bias tables were developed following guidance in the Cochrane Handbook. Two review authors assessed each included study and gave ratings of low, high or unclear risk of bias across seven criteria described below. Ratings of 'low risk of bias' are represented by green circles; 'high' by red; and 'unclear' by yellow. Numbers of participants are as at randomisation. Some trials with more than one active intervention appear in more than one graph.

Primarily pharmacological interventions

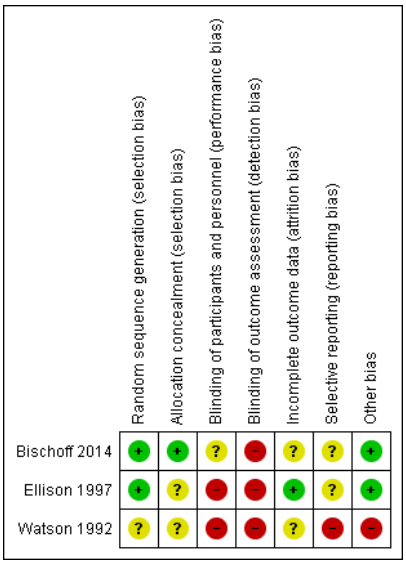
Antidepressants (4 studies; 177 participants)



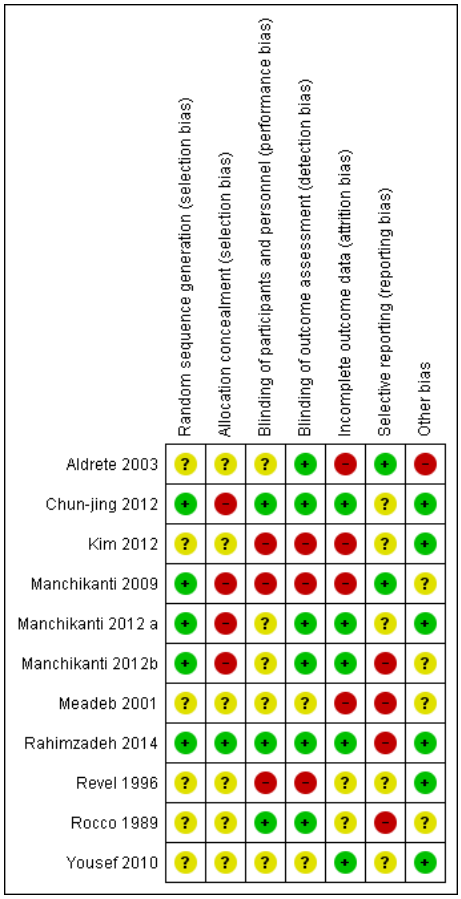
Antiepileptics (8 studies; 338 participants)



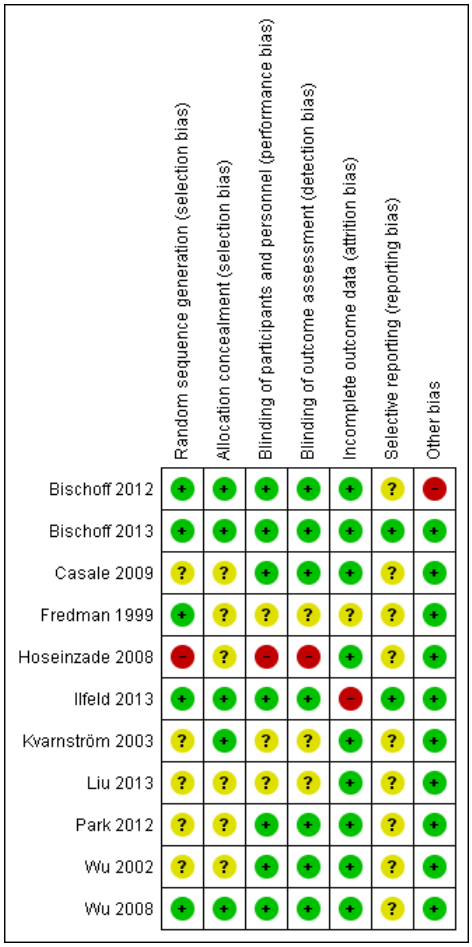
Capsaicin (3 studies; 174 participants)



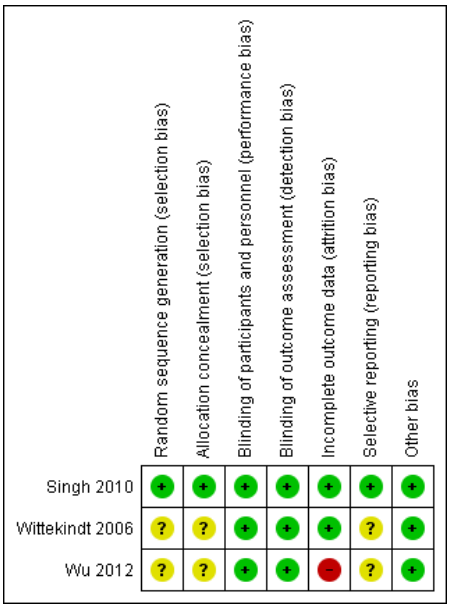
Epidural injections (11 studies; 886 participants)



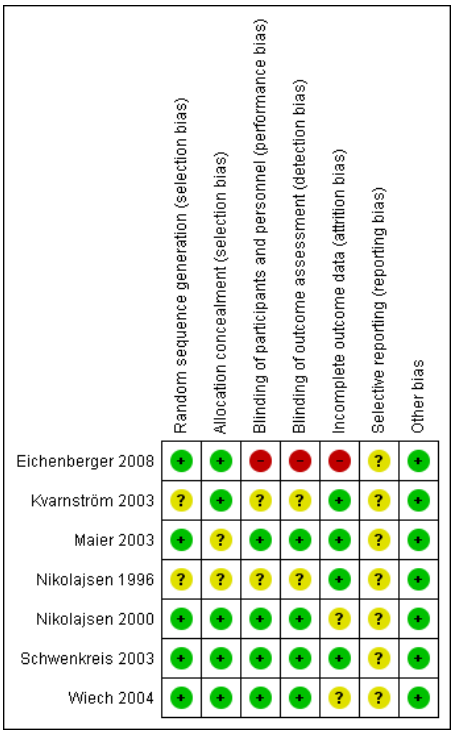
Local anaesthetic (11 studies; 324 participants)



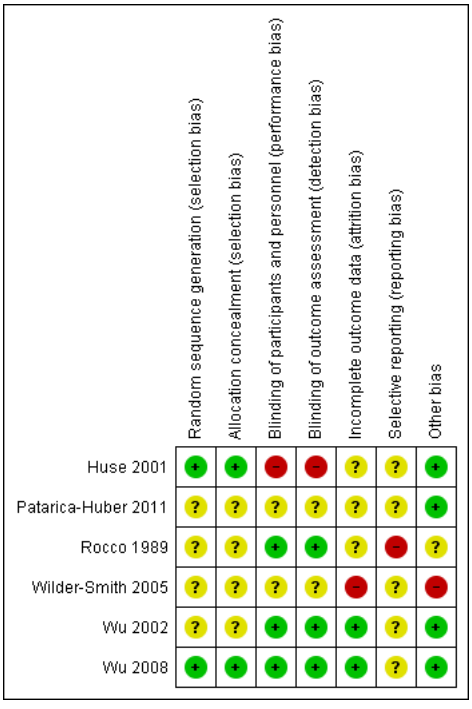
Neurotoxins (3 studies; 91 participants)



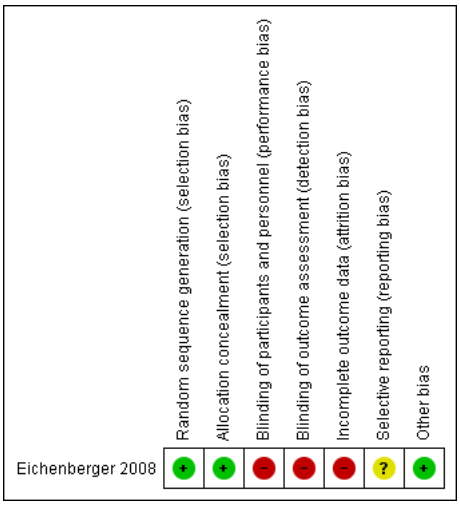
NMDA receptor antagonists (7 studies; 122 participants)



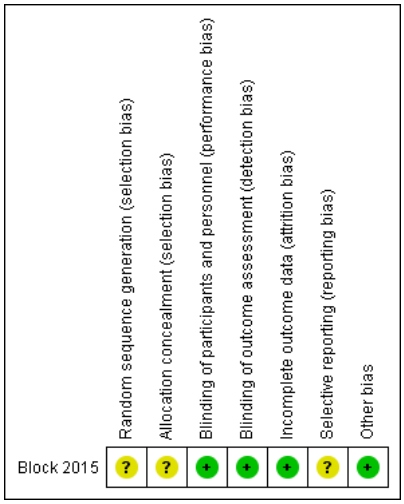
Opioids (6 studies; 297 participants)



Calcitonin (1 study; 20 participants)

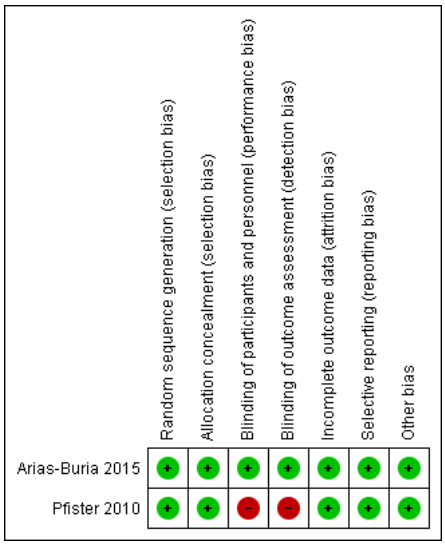


Naloxone adjuvant to morphine (1 study; 12 participants)

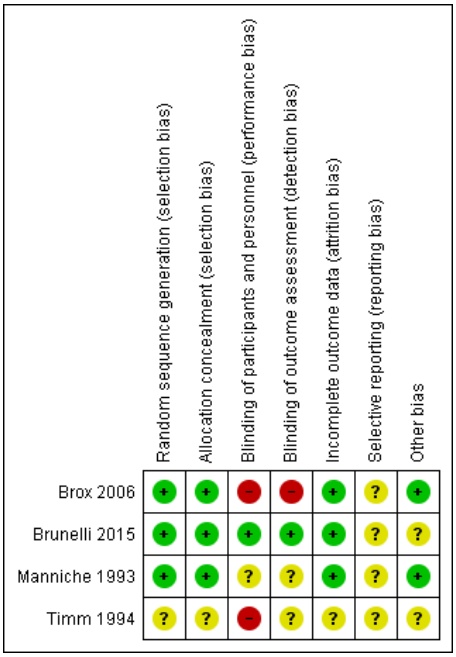


Primarily physical, surgical, psychological or other

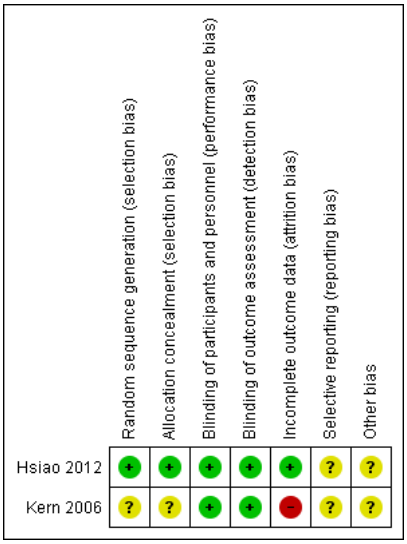
Acupuncture / dry needling (2 studies; 90 participants)



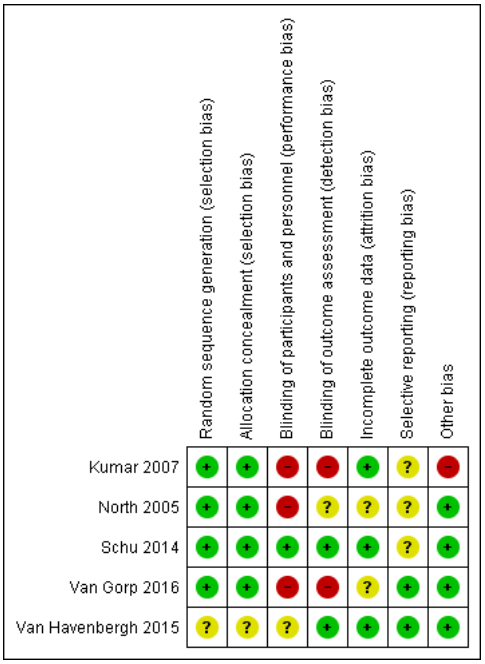
Exercise (4 studies; 323 participants)



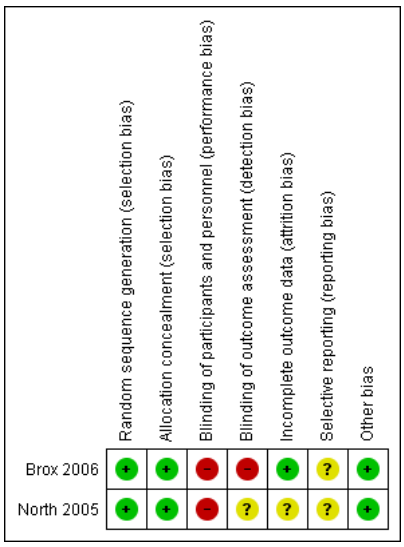
Limb covering (2 studies; 87 participants)



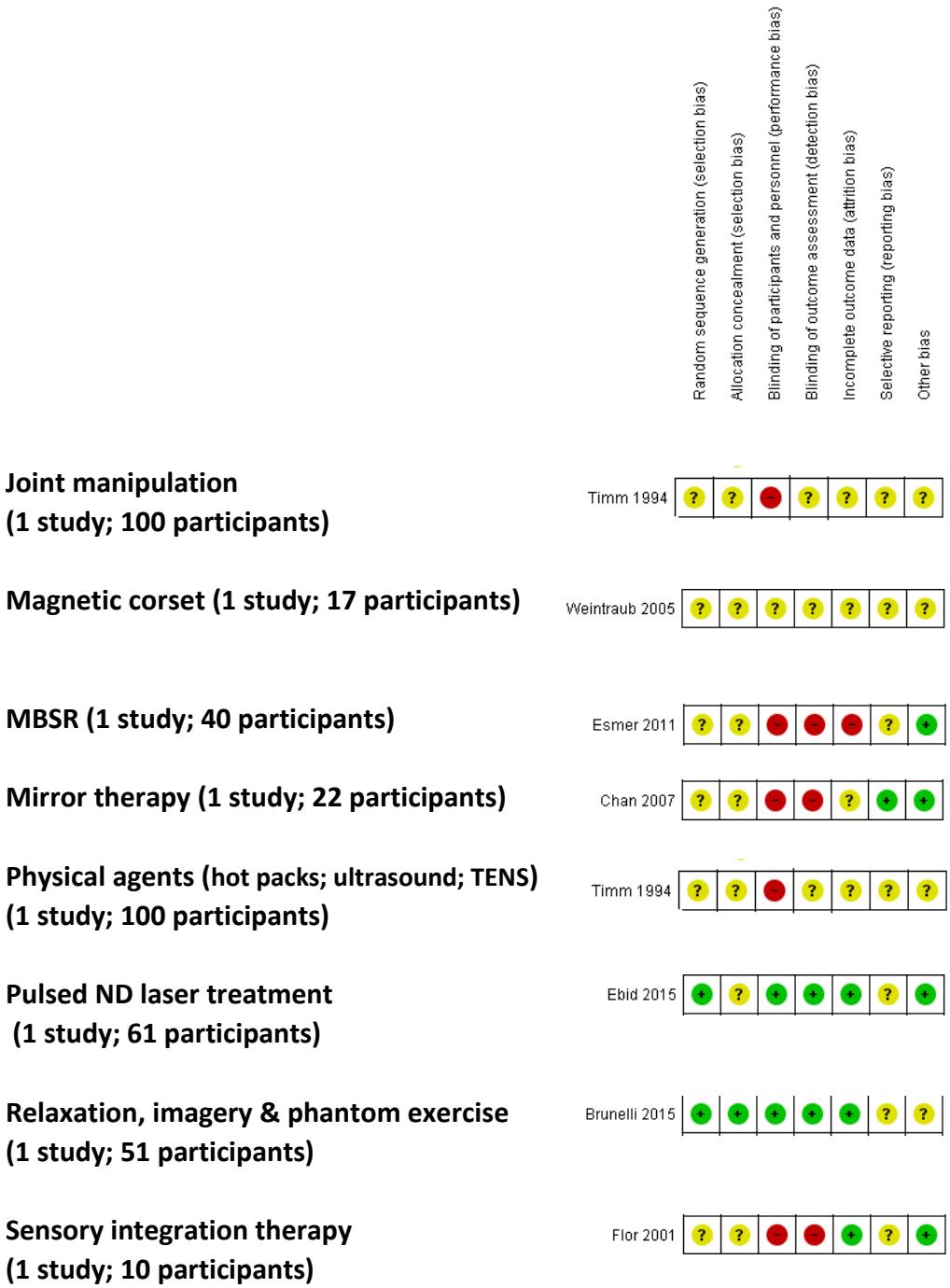
Spinal cord stimulation (5 studies; 260 participants)



Surgery (2 studies; 120 participants)



Other interventions (8) including:



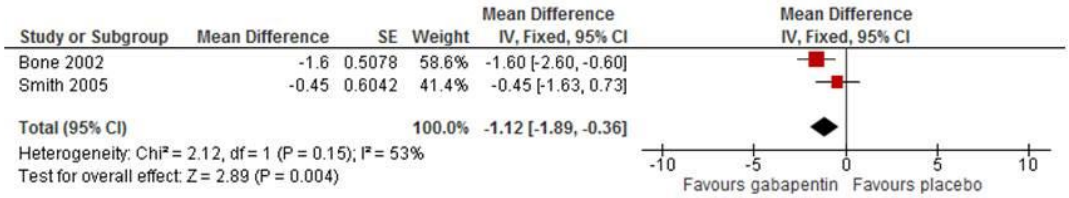


Fig. S1 Forest plot for trials of gabapentin *versus* placebo for treatment of chronic phantom limb pain

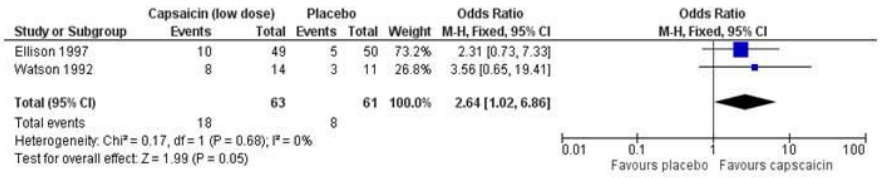


Fig. S2 Forest plot for trials of low-dose capsaicin *versus* placebo for treatment of chronic postsurgical pain after cancer surgery